REVIEW

# Hyponatraemia in clinical practice

**M Biswas, J S Davies**

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Hyponatraemia is defined as a serum sodium concentration below 135 mmol/l. It causes major diagnostic and management problems in practice. Hyponatraemic disorders are divided into euvolaemic, hypervolaemic and hypovolaemic. In the evaluation of the hyponatraemic patient, history taking should focus on identifying the potential cause, duration and symptomatology. Clinical examination should include assessment of volume status. Acute hyponatraemia of less than 48 h duration requires prompt correction. Treatment may involve hypertonic saline, isotonic saline and appropriate hormone replacement therapy depending on the aetiology. Chronic hyponatraemia should be treated with caution because of the risk of central pontine myelinolysis.

Hyponatraemia is the electrolyte disorder most commonly encountered in clinical practice, with a reported incidence of 15–30%.[1] It poses considerable diagnostic and management problems for clinicians. The condition has a multifactorial aetiology, and multiple causes of hyponatraemia may be identified in individual patients. In the acute setting, treatment often has to be initiated before a confirmatory diagnosis can be made and results of supportive biochemical investigations are available. Both over-correction and under-treatment can produce devastating effects on cerebral function.[2]

In this review, we will update the physiology of sodium and water balance and present a classification system of hyponatraemic disorders. Specific clinical scenarios and appropriate management strategies are provided.

## REGULATION OF SODIUM AND WATER BALANCE

Water homoeostasis is closely related to serum osmolarity and sodium concentration and is controlled by thirst, arginine vasopressin and the kidneys.[3] The normal plasma osmolarity is 275–295 mosm/l. Osmolarity is a measure of the osmotic pressure exerted by a solute in the presence of a semi-permeable membrane, which allows free passage of water without solute.[4] As cell membranes are highly permeable to water, lipids, anions and cations, the term ''tonicity'' is often used to mean ''effective osmolarity'' and the ability of a solution to result in a transmembrane shift in water.[4] Total plasma osmolarity does not always equal ''effective plasma osmolarity''.[5] For example, organic solutes such as urea, methanol and ethanol might increase serum osmolarity but can move freely in and out of cells and therefore do not induce a transcellular shift of water.[5 6]

The principle determinants of plasma osmolarity are sodium and anions such as bicarbonate and chloride.[5] This total concentration of anions and cations is roughly calculated as follows:

2 × (sodium mmol/l + potassium mmol/l) + urea mmol/l + glucose mmol/l.

If plasma osmolarity rises, antidiuretic hormone (ADH; also known as arginine vasopressin, AVP), a nonapeptide hormone synthesised in the hypothalamus and stored in the posterior pituitary, is released and thirst is activated.[1] AVP binds to the V2 receptor in the renal collecting ducts, which stimulates the synthesis of cyclic AMP which then activates protein kinase A. Protein kinase A induces the phosphorylation of the aquaporin 2 water channel.[7] Aquaporins are proteins which consist of membrane-spanning domains joined by connecting loops that fold back on to the membrane to form a pore, which allows water to pass.[7] Phosphorylation results in the translocation of intracytoplasmic aquaporin 2 water channels to the apical cell membrane and tubular water reabsorption.[7] In contrast, in healthy people, a large water load results in an acute fall in plasma AVP concentration and the excretion of large volumes of dilute urine.[8]

With an intact diluting mechanism, the kidney can excrete in excess of 10 litres per day, resulting in a maximally dilute urine of less than 100 mosm/l, protecting against hyponatraemia.[1] Thus the consumption of excessive volumes of water does not usually cause hyponatraemia unless intake exceeds 10–15 l/day, overwhelming the renal diluting mechanism.

The renin–angiotensin–aldosterone system also regulates sodium balance, through its effect on aldosterone. This mineralocorticoid hormone stimulates sodium reabsorption in the distal nephron and the distal colon via the amiloride-sensitive sodium channel and Na/K ATPase, the sodium pump.[3] Urinary excretion of sodium can vary from 1 mmol/day to up to 400 mmol/day depending on the amount of sodium ingested.[3]

## CLASSIFICATION OF HYPONATRAEMIA

Hyponatraemia is defined as a serum sodium concentration of <135 mmol/l after the exclusion of ''pseudo-hyponatraemia''. In the latter, increases in the non-aqueous components of plasma such as in hypertriglyceridaemia or hyperproteinaemia result in a spuriously low sodium

See end of article for authors' affiliations

Correspondence to: Dr J S Davies, Department of Medicine, University Hospital of Wales, Heath Park, Cardiff CF14 4XW, Wales, UK; daviesjs@cardiff.ac.uk

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**Abbreviations:** ADH, antidiuretic hormone; AVP, arginine vasopressin; CCF, congestive cardiac failure; EABV, effective arterial blood volume; SIADH, syndrome of inappropriate ADH secretion

**Box 1 Classification of hyponatraemic disorders**

**Hypovolaemic hyponatraemia: reduced extracellular fluid**
- Renal loss of sodium and water; urine Na >20 mmol/day
  - Causes:
    - Diuretic use
    - Salt wasting nephropathy
    - Cerebral salt wasting
    - Mineralocorticoid deficiency/adrenal insufficiency
    - Renal tubular acidosis
- Extrarenal loss of sodium and water with renal conservation; urine Na <20 mmol/day
  - Causes:
    - Burns
    - Gastrointestinal loss
    - Pancreatitis
    - Blood loss
    - 3rd space loss (bowel obstruction, peritonitis)

**Hypervolaemic hyponatraemia: expanded intracellular fluid and extracellular fluid but reduced effective arterial blood volume**
- Causes:
  - Congestive cardiac failure
  - Cirrhosis
  - Nephrotic syndrome

**Euvolaemic hyponatraemia: expanded intracellular and extracellular fluid but oedema absent**
- Causes:
  - Thiazide diuretics (can be euvolaemic or hypovolaemic)
  - Hypothyroidism
  - Adrenal insufficiency (can be euvolaemic or hypovolaemic)
  - SIADH (cancer, central nervous system disorders, drugs, pulmonary disease, nausea, postoperative pain, HIV, infection, Guillain-Barre syndrome, acute intermittent porphyria)
  - Decreased solute ingestion (beer potomania/tea and toast diet)

SIADH, syndrome of inappropriate antidiuretic hormone secretion.

concentration.[1] Hyponatraemic disorders are divided into euvolaemic, hypovolaemic and hypervolaemic (box 1).

A confusing number of descriptive terms such as hypotonic hyponatraemia and hypertonic hyponatraemia are also used in the literature in association with hyponatraemia.

Hypertonic hyponatraemia refers to the translocation of water from the intracellular compartment into the extracellular compartment, because of the presence of an osmotically active "hypertonic" solute in the plasma, which cannot enter cells. This is seen after mannitol administration after transurethral resection of the prostate[9] or insulinopenic states resulting in hyperglycaemia.[10]

Hypotonic hyponatraemia is also termed dilutional hyponatraemia and reflects water retention. Patients with hypotonic hyponatraemia can have normal or high serum osmolarity and be either euvolaemic or hypervolaemic.

**Box 2 Drugs that cause SIADH (not exhaustive, if in doubt consult product information leaflet)**

Carbamazepine
Chlorpropramide
Clofibrate
Cyclophosphamide
Desmopressin (AVP receptor agonist)
Ecstasy
Interferon
Mirtazipine
Nicotine
Omeprazole
Opiate derivatives
Oxytocin (AVP receptor agonist)
Phenothiazines
Prostaglandin synthesis inhibitors
Serotonin-reuptake inhibitors
Tricyclic antidepressants
Venlafaxine
Vincristine

AVP, arginine vasopressin; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

## EUVOLAEMIC HYPONATRAEMIA

This is the most commonly encountered form of hyponatraemia in hospital patients, and the syndrome of inappropriate ADH secretion (SIADH) is a diagnosis that is often made; but it is important to stress that the latter is a diagnosis of exclusion. The diagnostic criteria for SIADH are hyponatraemia with low serum osmolarity (<270 mosm/l) and an inappropriately high urine osmolarity of >100 mosm/kg in a euvolaemic patient in whom hypopituitarism, hypoadrenalism, hypothyroidism renal insufficiency and diuretic use have been excluded.[11]

In SIADH, excessive ADH release produces renal water reabsorption, and the body's intracellular and extracellular fluid compartments are expanded, resulting in hyponatraemia.[12] Despite the expansion of fluid compartments, the patient is not oedematous clinically and therefore the term euvolaemic is applied. SIADH is often caused by drugs (box 2).

Plasma AVP measured by radioimmunoassay would be increased in such cases, but this is of limited use in clinical practice because of the lack of availability.

## HYPOVOLAEMIC HYPONATRAEMIA

Diuretic-induced hyponatraemia is one of the most common causes of hypovolaemic hyponatraemia and is associated with high urinary sodium.[5, 13] Hyponatraemia occurs more commonly with thiazide diuretics, although it has also been

described in association with furosemide and spironolactone.[14] Thiazide diuretics act at the distal tubule. Mechanisms postulated for thiazide diuretic-induced hyponatraemia include hypovolaemia-stimulated ADH and interference with urinary dilution in the cortical diluting segment.[5] Some studies have identified specific risk factors for the development of hyponatraemia and these include: institutionalised elderly patients, low serum potassium concentration, low total body weight and indapamide use.[13, 15]

Salt-losing nephropathy occurs in patients with advanced chronic renal disease who are unable to conserve sodium and also in patients with proximal renal tubular acidosis and mild renal insufficiency. Salt-losing nephropathy may be seen in medullary cystic disease, polycystic kidney disease, analgesic nephropathy and obstructive uropathy.[5]

Hyponatraemia with extracellular fluid volume contraction and urine sodium >20 mmol/l in association with hyperkalaemia may also be due to mineralocorticoid deficiency. It is noteworthy that hyperkalaemia is not present in one-third of patients with Addison's disease.[3]

Cerebral salt wasting was first reported in 1950 by Peters *et al*[16] in three patients with neurological disorders, hyponatraemia, and clinical evidence of volume depletion and renal sodium wasting without disturbance of the pituitary adrenal axis. It is increasingly recognised in disorders of the central nervous system, particularly in the field of neurosurgery.[12, 17, 18] This phenomenon has often been reported in patients with subarachnoid haemorrhage who are found to be hyponatraemic, with raised urine sodium (>25 nmol/l) and high urine osmolarity.[17 18] Such patients fulfil laboratory criteria for SIADH, but have clinical signs of volume depletion, including low central venous pressure.[17] In one report total blood volume was measured and shown to be reduced.[17] The likely candidate hormones mediating renal sodium loss are brain natriuretic peptide and ouabain-like peptide.[19]

Gastrointestinal and third space losses may cause hyponatraemic hypovolaemia, but there is avid sodium retention by the kidneys. Urine sodium concentration is <10 mmol/l, and the urine is hyperosmolar.

## HYPERVOLAEMIC HYPONATRAEMIA

The three main causes of hypervolaemic hyponatraemia are congestive cardiac failure (CCF), cirrhosis and renal disease. In these cases, total body sodium is increased, but total body water (intracellular and extracellular fluid) is disproportionately expanded resulting in hyponatraemia and oedema.[20]

In CCF a fall in cardiac output and mean arterial pressure reduces effective arterial blood volume (EABV). This activates the sympathetic nervous system, decreases renal blood flow, and triggers release of AVP leading to water reabsorption in the collecting ducts.[21] Decreased renal blood flow stimulates the renin–angiotensin–aldosterone system, which enhances sodium reabsorption.[22] Hyponatraemia associated with CCF may also be exacerbated by diuretic therapy. Numerous studies have demonstrated that the development of hyponatraemia in this condition is a poor prognostic indicator.[23, 24]

In cirrhosis, many factors lower EABV and lead to hyponatraemia through similar mechanisms to those described above. Portal hypertension leads to fluid migration into the peritoneal cavity (ascites), and decreased serum albumin lowers plasma oncotic pressure. The damaged liver fails to degrade vasodilating factors, which reduces total peripheral resistance and causes splanchnic vasodilatation, reducing EABV. Diuretic administration, gastrointestinal haemorrhage and large volume paracentesis may exacerbate hyponatraemia in cirrhosis.[25, 26] Hyponatraemia is also indicative of poor prognosis and such patients are at higher risk of hepatorenal syndrome.[27]

In renal disease, proteinuria may lower plasma oncotic pressure and reduce EABV, triggering activation of the renin–angiotensin and aldosterone system and ADH release.[5] Hypervolaemic hyponatraemia may also result from defective renal salt and water excretion.[5]

## SPECIFIC CLINICAL SETTINGS

### Alcohol abuse

Hyponatraemia in this setting is beer potomania syndrome, and the diagnostic criteria include a history of binge drinking, poor dietary solute intake, and decreased sodium concentrations in the absence of other causes.[28] Urine osmolarity is <100 mosm/kg in this situation, indicating ADH suppression.[28] In addition to alcoholic liver disease, traumatic cerebral injury plus all the other disorders mentioned above may affect the alcoholic patient.

### Hyponatraemia in psychiatric disorders

SIADH can occur in the setting of acute psychosis and also after use of psychotropic medication.[29] Excessive water intake is often seen in association with psychiatric illness and is commonly referred to as psychogenic polydipsia.[30] High-volume water intake eventually overburdens the renal diluting mechanism. It is unclear what causes such compulsive drinking, but proposed mechanisms include hyperactivity of the hypothalamic thirst centre, neuroleptic drugs and resetting of the hypothalamic osmostat.[30]

### Marathon runners

Marathon-induced hyponatraemia is now emerging as a cause of race-related death. Hyponatraemia is caused by the consumption of high volumes (>3 litres) of fluid in excess of sodium losses.[31]

### Postoperative hyponatraemia

Careful assessment of admission notes, premedication, intraoperative records, fluid balance charts and anaesthetic records is imperative. Drug therapy, surgical procedures and pain are all causes of SIADH. Sodium picosulphate bowel preparation before colonic surgery may cause dehydration and electrolyte disorders, including hyponatraemia.[32] As previously mentioned, irrigation solutions such as mannitol, sorbitol and glycine may cause hypertonic hyponatraemia when absorbed.[9] The intravenous administration of large volumes of 5% dextrose is a common cause of postoperative hyponatraemia.

### Hyponatraemia in primary adrenal insufficiency (Addison's disease) and secondary adrenal insufficiency

Primary adrenal insufficiency is associated with glucocorticoid deficiency, which impairs renal water excretion and mineralocorticoid deficiency, which causes renal sodium loss.[1] Secondary adrenal insufficiency may be due to hypopituitarism. Glucocorticoid deficiency is the predominant cause of hyponatraemia in this setting, as mineralocorticoid activity is preserved. In addition, SIADH induced by hypothyroidism may contribute.[1] Hyponatraemia may resolve after correction of cortisol deficiency.[33]

### Symptoms of hyponatraemia

The symptoms are primarily neurological and relate to the rapidity of fall of serum sodium.[34] Acute hyponatraemia is defined as occurring within <48 h. There are usually no symptoms if serum sodium is 130–135 mmol/l. Nausea and malaise are seen if serum sodium falls to 125–130 mmol/l. Headaches, nausea, vomiting, muscle cramps, restlessness, disorientation and depressed reflexes can be seen if serum sodium falls below 125 mmol/l.[35] When severe hyponatraemia evolves over a period of hours, seizures, coma, permanent brain

**Table 1** Sodium content of infusates

| Infusate | Infusate sodium (mmol/l) | ECF distribution (%) |
|---|---|---|
| 5% | 855 | 100 |
| 3% | 513 | 100 |
| 0.9% | 154 | 100 |
| Ringer's lactate | 130 | 97 |
| 0.45% NaCl in water | 77 | 73 |
| 5% dextrose in water | 0 | 40 |

ECF, extracellular fluid.

damage, respiratory arrest, brain-stem herniation and death may occur.[6 35]

In sharp contrast, patients with chronic hyponatraemia are often asymptomatic irrespective of the degree of hyponatraemia.[1] Symptoms may only occur if there is acute exacerbation of hyponatraemia, or if serum sodium falls below 110 mmol/l.[1] In chronic hyponatraemia present for >48 h, the brain adapts to protect itself against cerebral oedema: a rapid increase in plasma sodium can lead to a decrease in brain cell volume with resultant demyelination.[36] It may not be apparent until 2–6 days after correction of sodium, and most patients are left with permanent neurological dysfunction including quadriplegia, pseudobulbar palsy and seizures.[34 36] Coma and death may occur. Individuals at particular risk include elderly patients on thiazides, alcoholics and patients with primary polydipsia.[1]

## Management of hyponatraemia

The treatment of hyponatraemia depends largely on its onset, aetiology and symptomatology. Initial evaluation of any patient with hyponatraemia involves identification of the onset of the condition (acute or chronic), the presence of symptoms and assessment of volume status.

A clinical history of renal, liver or cardiac disease should be noted, as well as previous electrolytes to distinguish acute from chronic hyponatraemia. Any loss of blood or extracellular fluid should be determined. A precise drug history, which includes recreational drug use, is necessary. Symptoms of headache, nausea, seizures and confusion suggest raised intracranial pressure.

On physical examination, an accurate recording of the patient's volume status is critical. The biochemical parameters in salt-wasting conditions and those in SIADH can be identical and are differentiated by determining volume status (box 3). For example, distinguishing cerebral salt wasting from SIADH is of vital importance, as fluid restriction in a volume-depleted patient may worsen ischaemic cerebral injury in subarachnoid haemorrhage.[19] Measurement of central venous pressure may be required.

The presence or absence of oedema, skin turgor and postural drop in systolic blood pressure of >20 mm Hg should all be recorded. When the patient cannot stand upright, sitting blood pressure can be used as an estimate. Examination may also reveal signs of an underlying illness causing hyponatraemia such as hypoadrenalism, hypopituitarism, chronic liver disease or nephrotic syndrome.

**Box 3 Biochemical parameters in hyponatraemia**

| EABV low | EABV normal |
|---|---|
| Urine Na>20 mmol/l | Urine Na>20 mmol/l |
| High urine osmolarity | High urine osmolarity |
| Low serum osmolarity | Low serum osmolarity |
| Diuretics | SIADH |
| Cerebral salt wasting | Adrenal insufficiency |
| Salt-losing nephropathy | Hypothyroidism |
| Mineralocorticoid deficiency | |

EABV, effective arterial blood volume; SIADH, syndrome of inappropriate ADH secretion

## Acute symptomatic hyponatraemia

It is agreed that in acute hyponatraemia (<48 h duration) prompt correction of serum sodium is required to reduce cerebral oedema. The risk of cerebral oedema from hyponatraemia in this setting is greater than the risk of central pontine myelinolysis from overcorrection.[34] It is also generally agreed that the correction of sodium should not exceed 1–2 mmol/h and 8 mmol/day on any given day of treatment.[1 6] The target should not be to normalise serum sodium, but to raise it to safe levels (>120 mmol/l) after which conservative measures such as fluid restriction can be deployed.[1]

Hyponatraemia from endocrine causes is treated with appropriate hormone replacement therapy. Management of hypertonic hyponatraemia secondary to hyperglycaemia should focus on insulin and isotonic fluid administration (table 1). Intravenous hydrocortisone (100 mg intravenously/intramuscularly four times a day for 24–48 h) is given to correct hyponatraemia when adrenal insufficiency is suspected, after blood samples for cortisol have been sent. Patients with hypovolaemic hyponatraemia should be treated with isotonic saline.[5 6]

In other situations where acute hyponatraemia develops in a euvolaemic or hypervolaemic patient with neurological symptoms, 3% sodium (3% NaCl) can be used.[5 6] Opinions differ with regard to its use, and there is no evidence for its superiority. If given, serum electrolytes should be measured hourly along with urine output and cardiovascular status. This regimen enables the rapid correction of hyponatraemia, with smaller volumes of fluid. Solute-free water should be completely withheld. Furosemide (40 mg intravenously) can be given in addition to promote solute-free water excretion.[5 6] Isotonic saline is unsuitable for correcting hyponatraemia in euvolaemic or hypervolaemic states, as the resulting rise in sodium is small and there is a net retention of water, potentially worsening hyponatraemia.[37]

The rate of infusion can be started at 1–2 ml/kg/h, with repeated hourly estimates of serum sodium. The Adrogue–Madias formula[6] may assist in providing ''the anticipated change in serum sodium'' following the administration of 1 litre of any infusate containing sodium:

Change in Na mmol/l = (Na in infusate − serum Na)/(total body water + 1)

Total body water is estimated from body weight and expressed in litres; it is roughly 0.5 × female weight in kg and 0.6 × male weight in kg. This equation has been evaluated recently in a large series of patients with dysnatraemias and accurately predicted changes in serum sodium in most patients, but underestimated the degree of sodium rise in certain cases.[38]

## Chronic hyponatraemia

Caution is advised in the treatment of chronic hyponatraemia, as the risk of osmotic demyelination is high because of brain adaptation; it may even develop with water restriction alone.[34–36] The goal of treatment of chronic asymptomatic hyponatraemia is to remove the underlying cause. If chronic hyponatraemia becomes symptomatic, treatment involves slow, gradual correction of sodium, largely with fluid restriction (800 ml/day) once hypovolaemia has been excluded.[5 6] If sodium fails to rise with fluid restriction, a reassessment of the patient's volume status should be made, and, if euvolaemic, demeclocycline 600–1200 mg/day can be given.[1 5 6] Most drug-induced hyponatraemia responds to withdrawal of the offending agent with or without fluid restriction.[6]

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### Oedematous states with low EABV

In severe cardiac failure, treatment should focus on sodium and water restriction and the administration of loop diuretics, which will reduce the action of ADH on the collecting tubules and limit water reabsorption.[14] Spironolactone may promote the excretion of oedema fluid while maintaining potassium.[14] Thiazide diuretics should be avoided, as they impair urinary dilution and can paradoxically worsen hyponatraemia.[5]

In cirrhosis, hyponatraemia is usually treated with salt and water restriction. When overdiuresis is causative, diuretics are temporarily terminated. Some have treated sodium deficits with 3% saline, furosemide-induced diuresis, and re-infusion of solute.[39]

## FUTURE THERAPIES

The aquaretics are a new line of agents which hold promise for future use in the treatment of euvolaemic and hypervolaemic hyponatraemia. Vasopressin receptor antagonists block AVP from binding to V2 receptors in the distal nephron and promote the excretion of electrolyte-free water.[40] In recent randomised trials, tolvaptan, an orally active V2 receptor antagonist, has been effective in raising serum sodium in euvolaemic and hypervolaemic subjects.[41] Conivaptan is another agent that shows activity at both the V2 receptor and the V1a receptor, which is responsible for AVP-mediated vasoconstriction. Dual receptor activity reduces cardiac preload and total peripheral resistance, which are both of benefit in CCF.[42]

## MULTIPLE CHOICE QUESTIONS (ANSWERS AFTER THE REFERENCES)

### Choose the best response out of the five options provided

1. Which of the following statements best describes the mechanism by which mannitol causes hyponatraemia?

(A) hypotonic hyponatraemia
(B) isotonic hyponatraemia
(C) reducing renal free water clearance
(D) hypertonic hyponatraemia
(E) increased urine sodium excretion

2. In which one of the following situations is urine sodium excretion likely to be less than 20 mmol/day?

(A) SIADH
(B) renal disease
(C) acute diarrhoea
(D) hyperglycaemia
(E) hypothyroidism

3. An elderly lady presents to A&E with an acute confusional state. She is pyrexial. Blood pressure is 140/90 and there is no postural drop. She takes carbamazepine for trigeminal neuralgia. Serum sodium is 123 mmol/l (135–145). Which of the following statements best applies to the diagnosis and management?

(A) acute hyponatraemia is the most probable cause of her confusion
(B) carbamazepine is an unlikely cause of hyponatraemia
(C) hypertonic saline should be used to correct hyponatraemia
(D) she may have acute on chronic hyponatraemia
(E) fluid restriction is the only treatment required in this setting

4. Which of the following best describes the mechanism of hyponatraemia in secondary adrenal insufficiency ?

(A) renal sodium wasting
(B) extra-renal sodium loss
(C) hypovolaemic hyponatraemia
(D) hypertonic hyponatraemia
(E) impaired renal water excretion

5. Which of the following best describes the action of the aquaretic agents?

(A) they bind to V1a receptors
(B) they act at the proximal convoluted tubule
(C) they bind to V2 receptors in the distal nephron and promote the excretion of sodium and water
(D) tolvaptan binds to the V2 receptor in the distal nephron
(E) tolvapatan demonstrates activity at the V1a receptor and the V2 receptor


### Authors' affiliations

**M Biswas,** Department of Medicine, Royal Gwent Hospital, Newport, Wales, UK
**J S Davies,** Department of Medicine, University Hospital of Wales, Heath Park, Cardiff, Wales, UK


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## ANSWERS

1. (D) Hypertonic hyponatraemia is the result of mannitol, an osmotically active substance entering the plasma and inducing a transcellular shift in water.

2. (C) In acute diarrhoea there is extrarenal sodium and water loss, with renal sodium conservation.

3. (D) SIADH secondary to carbamazepine can cause chronic hyponatraemia. Acute on chronic hyponatraemia may be the result of infection. Withdrawal of carbamazepine and treatment of infection are important therapeutic strategies in addition to fluid restriction.

4. (E) Impaired renal water excretion is the result of glucocorticoid deficiency.

5. (D) Tolvaptan is an antagonist at the V2 receptor in the distal nephron and it promotes electrolyte-free water clearance.